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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/424,629	Applicant(s) Simon Foote et al.
	Examiner Arun Chakrabarti	Art Unit 1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jul 9, 2001 .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-18 and 24-32 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-18 and 24-32 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant elected Group I, corresponding to claims 1-18 and 24-32, with traverse. The traversal is on the ground(s) that there is no burden in examining the claims of Groups I, II and III. This is not found persuasive because as the restriction makes clear, additional search of Groups II and III would require review of the patents in Groups II and III . Review of these additional searches is prima facie evidence of burden which is not rebutted.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 10, 14, and 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 10, the phrase "capable of" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

5. Claims 1-5 and 24-28 are rejected under 35 U.S.C. 102 (e) as being anticipated by Kamb (U.S. Patent 5,985,619) (February 9, 1999).

Kamb teaches a method of detecting a difference of one or more nucleotides between a nucleic acid molecule to be tested and a reference nucleic acid molecule and identifying a mutation (Abstract) , the method comprising:

subjecting the test nucleic acid molecule to base specific cleavage to generate oligonucleotide fragments (Claims 1-3 and 5 and Example IV, Column 6, line 50 to column 8, line 37);

separating the resulting oligonucleotide fragments based on mass by MALDI-TOF MS to produce a fingerprint of the oligonucleotide fragments comprising one or more peaks wherein a peak represents the mass of each fragment (Tables II and III and Example IV, Column 6, line 50 to column 8, line 37); and

identifying an altered peak relative to a reference nucleic acid molecule subjected to the same procedure wherein the presence of an altered peak is indicative of a difference of one or more nucleotides in the tested nucleic acid molecule (Claims 1 and 3 and Table II).

Kamb teaches a method wherein the nucleic acid molecule to be tested is amplified by a PCR prior to base specific cleavage (Column 4, lines 36-46 and Column 7, lines 39-54).

Kamb teaches a method wherein the base specific cleavage results in oligonucleotide fragments of from about 2 bases to about 1000 bases (Table III).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-7 and 24-30 are rejected under 35 U.S.C. 103 (a) over Kamb (U.S. Patent 5,985,619) (February 9, 1999) in view of Sutherland et al. (U.S. Patent 5,985,619) (November 16, 1999).

Kamb teaches the method of claims 1-5 and 24-28 as described above.

Kamb does not teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase.

Sutherland et al. teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase (Column 9, lines 4-29).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the mass spectrometry to assess DNA sequence polymorphisms of Kamb, since Sutherland et al. state, "The glycosylase useful in the present invention are those that specifically cleave unconventional bases, i.e., bases other than A,G,C or T in DNA and A,G,C and U in RNA. Glycosylases that specifically cleave unconventional bases such as N-& methylguanine, 3-methyladenosine, uracil and hypoxanthine are known to one of ordinary skill in the art. Preferred glycosylases include uracil N-glycosylase (UNG), hypoxanthine-DNA glycosylase, and 3-methyladenine-DNA glycosylases I and II. The most preferred glycosylase in accordance with present invention is UNG. UNG is commercially available (Column 9, lines 4-19)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the uracil specific base cleavage mediated by uracil-N-

glycosylase of Sutherland et al. into the mass spectrometry to assess DNA sequence polymorphisms of Kamb in order to improve the sequencing of nucleic acids containing unconventional bases. An ordinary practitioner would have been motivated to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the mass spectrometry to assess DNA sequence polymorphisms of Kamb in order to achieve the express advantages noted by Sutherland et al., of a preferred glycosylase UNG which is commercially available and useful to specifically cleave unconventional bases.

8. Claims 1-5, 10, 14 and 24-28 are rejected under 35 U.S.C. 103 (a) over Kamb (U.S. Patent 5,985,619) (February 9, 1999) in view of Koster (U.S. Patent 6,074,823) (June 13, 2000).

Kamb teaches the method of claims 1-5 and 24-28 as described above.

Kamb does not teach the method of using a computer capable of controlling a method of detecting mutation by MALDI-TOF MS.

Koster teach the method of using a computer capable of controlling a method of detecting mutation by MALDI-TOF MS (Column 5, lines 22-35).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a computer capable of controlling a method of detecting mutation by MALDI-TOF MS of Koster into the mass spectrometry to assess DNA sequence polymorphisms of Kamb, since Koster states, "An additional advantage of mass spectrometric sequencing is that the identified masses can be registered automatically by a computer and, by adding the time coordinate, automatically aligned to sequences. Since the

sequences so determined are memorized (i.e., saved to disk or resident in the computer memory), appropriate existing computer programs operating in a multitasking environment can be searching in the "background" (i.e., during continuous generation of new sequence data by the exonuclease mass spectrometric sequencer) for overlaps and generate contiguous sequence information which, via a link to a sequence data bank, can be used in homology searches, etc (Column 5, lines 22-35)." By employing scientific reasoning, an ordinary artisan would have combined and substituted a computer capable of controlling a method of detecting mutation by MALDI-TOF MS of Koster into the mass spectrometry to assess DNA sequence polymorphisms of Kamb in order to improve the sequencing of nucleic acids by automated procedures. An ordinary practitioner would have been motivated to combine and substitute a computer capable of controlling a method of detecting mutation by MALDI-TOF MS of Koster into the mass spectrometry to assess DNA sequence polymorphisms of Kamb in order to achieve the express advantages noted by Koster, of mass spectrometric sequencing by which the identified masses can be registered automatically by a computer and, by adding the time coordinate, automatically aligned to sequences and since the sequences so determined are memorized (i.e., saved to disk or resident in the computer memory), appropriate existing computer programs operating in a multitasking environment can be searching in the "background" (i.e., during continuous generation of new sequence data by the exonuclease mass spectrometric sequencer) for overlaps and generate contiguous sequence information which, via a link to a sequence data bank, can be used in homology searches, etc

9. Claims 1-5, 8-9, 11-13, 24-28 and 31-32 are rejected under 35 U.S.C. 103 (a) over Kamb (U.S. Patent 5,985,619) (February 9, 1999) in view of Caprioli (U.S. Patent 5,808,300) (September 15, 1998).

Kamb teaches the method of claims 1-5 and 24-28 as described above.

Kamb does not teach the method of subjecting fragmentation products to further separation by the post source decay method.

Caprioli teaches the method of subjecting fragmentation products to further separation by post source decay method (Column 3, lines 9-11).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a further separation by post source decay method of Caprioli into the mass spectrometry to assess DNA sequence polymorphisms of Kamb , since Caprioli states, "The use of post-source decay techniques is shown in order to obtain sequence verification (Column 3, lines 9-11)." By employing scientific reasoning, an ordinary artisan would have combined and substituted a further separation by post source decay method of Caprioli into the mass spectrometry to assess DNA sequence polymorphisms of Kamb in order to improve the sequencing of nucleic acids. An ordinary practitioner would have been motivated to combine and substitute a further separation by post source decay method of Caprioli into the mass spectrometry to assess DNA sequence polymorphisms of Kamb in order to achieve the express advantages, as noted by Caprioli, of a method which is used in order to obtain sequence verification.

10. Claims 1-5, 10, 14 , 16 and 24-28 are rejected under 35 U.S.C. 103 (a) over Kamb (U.S. Patent 5,985,619) (February 9, 1999) in view of Koster (U.S. Patent 6,074,823) (June 13, 2000) further in view of Sutherland et al. (U.S. Patent 5,985,619) (November 16, 1999).

Kamb in view of Koster teach the method of claims 1-5, 10, 14 and 24-28 as described above.

Kamb in view of Koster do not teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase.

Sutherland et al. teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase (Column 9, lines 4-29).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of Koster, since Sutherland et al. state, "The glycosylase useful in the present invention are those that specifically cleave unconventional bases, i.e., bases other than A,G,C or T in DNA and A,G,C and U in RNA. Glycosylases that specifically cleave unconventional bases such as N-& methylguanine, 3-methyladenosine, uracil and hypoxanthine are known to one of ordinary skill in the art. Preferred glycosylases include uracil N-glycosylase (UNG), hypoxanthine-DNA glycosylase, and 3-methyladenine-DNA glycosylases I and II. The most preferred glycosylase in accordance with present invention is UNG. UNG is commercially available (Column 9, lines 4-19)." By employing scientific

reasoning, an ordinary artisan would have combined and substituted the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of Koster in order to improve the sequencing of nucleic acids containing unconventional bases. An ordinary practitioner would have been motivated to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of Koster in order to achieve the express advantages noted by Sutherland et al., of a preferred glycosylase UNG which is commercially available and useful to specifically cleave unconventional bases.

11. Claims 1-5, 8-9, 11-13, 15, 24-28 and 31-32 are rejected under 35 U.S.C. 103 (a) over Kamb (U.S. Patent 5,985,619) (February 9, 1999) in view of Caprioli (U.S. Patent 5,808,300) (September 15, 1998)further in view of Sutherland et al. (U.S. Patent 5,985,619) (November 16, 1999).

Kamb in view of Caprioli teach the method of claims 1-5, 8-9, 11-13, 24-28 and 31-32 as described above.

Kamb in view of Caprioli do not teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase.

Sutherland et al. teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase (Column 9, lines 4-29).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of Caprioli, since Sutherland et al. state, "The glycosylase useful in the present invention are those that specifically cleave unconventional bases, i.e., bases other than A,G,C or T in DNA and A,G,C and U in RNA. Glycosylases that specifically cleave unconventional bases such as N-& methylguanine, 3-methyladenosine, uracil and hypoxanthine are known to one of ordinary skill in the art. Preferred glycosylases include uracil N-glycosylase (UNG), hypoxanthine-DNA glycosylase, and 3-methyladenine-DNA glycosylases I and II. The most preferred glycosylase in accordance with present invention is UNG. UNG is commercially available (Column 9, lines 4-19)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of Caprioli in order to improve the sequencing of nucleic acids containing unconventional bases. An ordinary practitioner would have been motivated to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of Caprioli in order to achieve the express advantages noted by Sutherland et al., of a preferred glycosylase UNG which is commercially available and useful to specifically cleave unconventional bases.

12. Claims 1-5, 10, 14, 16-18 and 24-28 are rejected under 35 U.S.C. 103 (a) over Kamb (U.S. Patent 5,985,619) (February 9, 1999) in view of Koster (U.S. Patent 6,074,823) (June 13, 2000) further in view of Caprioli (U.S. Patent 5,808,300) (September 15, 1998).

Kamb in view of Koster teach the method of claims 1-5, 10, 14 , 16 and 24-28 as described above.

Kamb in view of Koster do not teach the method of subjecting fragmentation products to further separation by the post source decay method.

Caprioli teaches the method of subjecting fragmentation products to further separation by post source decay method (Column 3, lines 9-11).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a further separation by post source decay method of Caprioli into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of Koster, since Caprioli states, "The use of post-source decay techniques is shown in order to obtain sequence verification (Column 3, lines 9-11)." By employing scientific reasoning, an ordinary artisan would have combined and substituted a further separation by post source decay method of Caprioli into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of Koster in order to improve the sequencing of nucleic acids. An ordinary practitioner would have been motivated to combine and substitute a further separation by post source decay method of Caprioli into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kamb in view of

Koster in order to achieve the express advantages, as noted by Caprioli, of a method which is used in order to obtain sequence verification.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Arun Chakrabarti,

Patent Examiner,

August 16, 2001

JEFFREY FREDMAN
PRIMARY EXAMINER